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Research Submission

Ketamine Infusions for Treatment Refractory Headache

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Background.—Management of chronic migraine (CM) or new daily persistent headache (NDPH) in those who require aggressive outpatient and inpatient treatment is challenging. Ketamine has been suggested as a new treatment for this intractable population.

Methods.—This is a retrospective review of 77 patients who underwent administration of intravenous, subanesthetic ketamine for CM or NDPH. All patients had previously failed aggressive outpatient and inpatient treatments. Records were reviewed for patients treated between January 2006 and December 2014.

Results.—The mean headache pain rating using a 0-10 pain scale was an average of 7.1 at admission and 3.8 on discharge ($P < .0001$). The majority (55/77, 71.4%) of patients were classified as acute responders defined as at least 2-point improvement in headache pain at discharge. Some (15/77, 27.3%) acute responders maintained this benefit at their follow-up office visit but sustained response did not achieve statistical significance. The mean length of infusion was 4.8 days. Most patients tolerated ketamine well. A number of adverse events were observed, but very few were serious.

Conclusions.—Subanesthetic ketamine infusions may be beneficial in individuals with CM or NDPH who have failed other aggressive treatments. Controlled trials may confirm this, and further studies may be useful in elucidating more robust benefit in a less refractory patient population.

Key words: ketamine, headache, chronic migraine, new daily persistent headache

Abbreviations: CM chronic migraine, CRPS complex regional pain syndrome, DHE dihydroergotamine, IV intravenous, NDPH new daily persistent headache, NSAIDs non-steroidal anti-inflammatory drugs

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BACKGROUND

Ketamine is a phencyclidine derivative antagonist of NMDA receptors that is most commonly employed as an anesthetic agent. When given at a subanesthetic dose, ketamine may be safe and effective in treatment of a variety of pain disorders, opioid tolerant patients, and depression. Antagonism of glutamate and excitatory neurotransmission decreases central sensitization and pain in animal studies and may alleviate chronic pain disorders such as chronic daily headache and fibromyalgia.[1,2] Chronic use of NMDA antagonists such as memantine and amantadine may be useful in headache prevention.[3,4]

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A randomized controlled study and case report have investigated the effectiveness of ketamine nasal spray for prolonged aura or hemiplegic migraine.[5,6] A few case series report using intravenous ketamine for the treatment of chronic daily headache.[7]

Subanesthetic ketamine administration has been suggested to be useful in treatment of other pain disorders such as complex regional pain syndrome (CRPS), fibromyalgia, and acute on chronic pain with opioid tolerance. In a randomized, double-blind trial involving 60 patients, Sigtermans et al reported improvement in CRPS patients treated with continuous, subanesthetic infusions of ketamine for 4 days with improvement maintained 11 weeks following the infusion.[8] Another randomized, double-blind study of 19 patients suggested improvement with subanesthetic ketamine when dosed below 0.35 mg/kg/hr and administered once daily for 4 hours on 10 consecutive days.[9] Additional open label and observational studies have suggested benefit in the CRPS patient population.[10,11] Reports of subanesthetic ketamine use in treatment of fibromyalgia include a randomized double-blind crossover study suggesting benefit with ketamine administered at 0.3 mg/kg over 30 minutes, and a double-blind controlled study with 11 patients receiving ketamine administered 0.3 mg/kg over 10 minutes demonstrating pain reduction following infusions.[12,13]

We report our use of subanesthetic ketamine in patients with refractory chronic headache disorders who have failed other aggressive treatments. Since January 2006, we have administered subanesthetic ketamine to dozens of patients with refractory, chronic headache. The clinical dosing schedule and monitoring at our institution was developed by the department of anesthesiology for use in palliative care, CRPS, and acute pain in the presence of opioid tolerance and directly adopted for use in our patients.

METHODS

We conducted a retrospective review of patients admitted to Thomas Jefferson University Hospital who received intravenous ketamine for chronic migraine (CM) or new daily persistent headache (NDPH) between January 2006 and December 2014. Patients were identified by querying our institution's inpatient electronic physician order entry software for all individuals who were admitted by a physician in our practice and treated with intravenous ketamine. This list was cross-referenced to our outpatient electronic medical record by hand to verify a diagnosis of chronic migraine or new daily persistent headache. Inpatient records were examined for details on treatments (ie, specific medications, doses, and durations) and their results (ie, pain relief and adverse events). Outpatient records were examined for post-hospitalization patient status with respect to pain relief. Comorbid diagnoses were also noted. All data were recorded by hand into a Microsoft Excel database for analysis.

All patients selected to undergo ketamine administration had daily or continuous headaches and had failed not only numerous adequate trials of highly recommended preventive and acute therapies but also other aggressive inpatient treatments including intravenous (IV) dihydroergotamine (DHE), (IV) lidocaine, neuroleptics, and non-steroidal anti-inflammatory drugs (NSAIDs) in at least one past hospitalization. Most patients also had failed at least one series of nerve blocks utilizing lidocaine and bupivacaine to block both greater occipital nerves and trigeminal branches. In most cases, patients had been hospitalized for headache several times before. Migraine preventive medications and medications for other medical conditions were continued during ketamine treatment. Patients selected to undergo ketamine infusion were admitted to the hospital specifically for IV ketamine due to refractory nature of their headaches and failed interventions described above. Our ketamine admissions do not utilize a comprehensive approach with psychological support and educational strategies as selected patients have already undergone such interventions in their previous hospitalizations.

Prior to initiation of ketamine infusion, all patients had lab testing including basic metabolic panel, complete blood count, coagulation studies, thyroid testing, and markers of inflammation. Most

patients also had baseline hepatic function testing. Ketamine was the only new acute therapy administered upon admission (with one exception, noted in results). Some patients did receive additional acute medications that had been previously used for their headaches. Specifically, 12 patients received dihydroergotamine, 40 received IV neuroleptics, and 28 received IV NSAIDs.

At our institution, ketamine is administered by protocol under direction of the department of anesthesiology and managed by specially trained in-house pain nurses. We use the following general dosing schedule: ketamine is initiated at 0.1 mg/kg/hr, and can be increased by 0.05 mg/kg/hr hourly until pain relief, nystagmus, or mild inebriation. When an infusion rate of 0.25 mg/kg/hr is achieved, the rate is maintained for 6 hours to assess for side effects before further dose increase. If mild inebriation or nystagmus creating bothersome visual side effect is present, the ketamine dose is not increased until symptoms improve. If side effects are intolerable, the dose is reduced. If pain relief is inadequate, the dose is titrated to effect. We generally limit the maximum dose to 1 mg/kg/hr. Ketamine is infused continuously in this fashion for a maximum of 5 days total. (There was one exception to this, noted in results.) Patients receive frequent monitoring of vital signs, pain, and sedation assessment. Patients are routinely questioned regarding occurrence of adverse events (AEs) such as nausea, vomiting, vivid dreams, hallucinations, paranoia, tremors, visual changes, and confusion. In an effort to reduce side effects, patients commonly are also administered medications such as transdermal clonidine, benzodiazepines, and antiemetics. Patients receiving this ketamine titration protocol are managed on standard floors with standard monitoring. However, it is important to note that assessment and titration is managed by a highly experienced team of specially trained pain nurses who are in-house around the clock. There is also a high degree of communication between the anesthesiology pain management physicians and neurologists.

Patients were defined according to treatment response. Acute responders were those who had at least 2-point improvement in headache based on the 11-point 0-10 verbal pain rating scale when comparing admission headache assessment to discharge headache assessment. This choice was made based on the principle that a 1.5-point reduction in pain is considered clinically significant and meaningful.[14] Sustained responders were those who had ongoing 2-point improvement in headache assessment when admission pain level was compared with their average reported headache assessment at the first follow-up office visit within one month of the admission date.

We obtained approval from our university Institutional Review Board for this retrospective study prior to review. The requirement for written informed consent was waived. Data were extracted by one reviewer. Patients were informed of the off-label nature of treatment prior to initiation of ketamine infusions.

Statistical Analysis.—Data were analyzed using GraphPad software. Two-tailed paired *t*-tests were used to compare admission pain scores to those at discharge and first outpatient follow-up. A subgroup analysis composed of two-tailed *t*-tests to compare acute and sustained response rates of CM and NDPH populations. A P value of $<.05$ was considered significant.

RESULTS

A total of 82 unique patients were admitted to Thomas Jefferson University Hospital by our practice and treated with subanesthetic ketamine during the aforementioned timeframe; 77 of these for medically refractory CM or NDPH (the remainder were treated for chronic cluster headache or visual snow). Our patients were aged between 18 and 65 years with a mean of 40.6 years. Twenty of our patients were men and 57 were women. Seventy-one of our patients identified themselves as having Caucasian ancestry and 6 as having African ancestry. Our patients included 63 patients with CM and 14 patients with NDPH, 13 of whom had a CM phenotype. About half (37/77, 48%) of patients met criteria for medication-overuse headache.

Most patients had multiple comorbidities, and many patients had at least one Axis I psychiatric diagnosis from the *Diagnostic and Statistical*

Table 1.—Comorbid Conditions Noted in Patients

Comorbid Condition	n (%)
Major depressive disorder	36 (46.8%)
Insomnia	36 (46.8%)
Adjustment disorder	27 (35.1%)
Fibromyalgia	17 (22.1%)
Generalized anxiety disorder	15 (19.5%)
Chronic back pain	9 (11.7%)
Irritable bowel syndrome	8 (10.4%)
Bipolar disorder	7 (9.1%)
Panic disorder	7 (9.1%)
Arthritis	6 (7.8%)
Restless leg syndrome	5 (6.5%)
Endometriosis	5 (6.5%)
Dysthymic disorder	3 (3.9%)
Endometriosis	3 (3.9%
Post-traumatic stress disorder	2 (2.6%)
Schizoaffective disorder	1 (1.3%)
None of the above comorbidities	2 (2.6%)

Manual of Mental Disorders—IV. All patients met with a psychologist or psychiatrist prior to hospitalization. Comorbid conditions that were extracted from analysis of the diagnostic codes attached to the patients' headache clinic charts are listed in Table 1.

The length of ketamine infusion ranged between 2 and 9 days, mean 4.8 days. After initiation, the ketamine rate (mg/kg/hr) ranged from 0.08 to 1.25, with a mean of 0.53. AEs were generally minimal and resolved with decrease in rate of ketamine infusion, but some patients did experience more significant adverse events (Table 2). Notably, one patient had to have the ketamine infusion stopped due to development of suicidality. Six patients developed unsteady gait during the infusion, and a further two patients experienced falls. One patient had a noted increase in liver enzymes from aspartate aminotransferase of 14 and alanine transaminase of 7 on admission to respective peaks of 172 and 134, which subsequently returned to baseline in outpatient follow-up.

The mean and range assessment of headache pain level on admission were 7.1 (2-10), and on discharge were 3.8 (2-10) for all patients. Analysis by paired *t*-test was significant ($P < .0001$) and estimated a mean difference of 3.253 (95% CI 2.60-3.90). Fifty-five (71.4%) patients were classified as acute responders, and among this group mean and range headache pain assessment were 7.1 (2-10) on admission and 2.5 (0-10) on discharge. The paired *t*-test for responders was also significant ($P < .0001$), and the mean difference was 4.573 (95% CI 3.99-5.15). Of the acute responders, 15 (27.3%) maintained improvement to be classified as sustained responders at their follow-up office visit with mean headache and range pain assessment at follow-up of 5.2 (2-7). The mean difference was 2.633 (95% CI 1.92-3.34), but the 95% confidence interval did not achieve significance based off of our predefined criteria of a 2-point reduction.

A subgroup analysis was performed to investigate differences between those patients hospitalized for NDPH compared with those treated for CM. Analysis was again carried out using paired *t*-test. Eight out of 14 (57.1%) NDPH patients were acute responders with a mean difference of 4.25 (95% CI 2.59-5.91) ($P < .0005$). Of these, 4 (50%) went on to maintain response with mean difference of 2.5(95% CI 0.91-4.09) ($P < .0154$). Of the CM patients, 47 (74.6%) were acute responders with a mean

Table 2.—Adverse Events Among Patients

Adverse Event	n (%)
Diplopia or blurred vision	28 (36.4%)
Confusion	19 (24.7%)
Hallucinations	16 (20.8%)
Dysarthria	9 (11.7%)
Dizziness	9 (11.7%)
Vivid dreams	7 (9.1%)
Sedation	7 (9.1%)
Unsteady gait	6 (7.8%)
Worsened nausea	5 (6.5%)
Emotional lability	5 (6.5%)
Urinary retention	4 (5.2%)
New onset insomnia	2 (2.6%)
Fall	2 (2.6%)
Incontinence	1 (1.3%)
Suicidality	1 (1.3%)
Liver enzyme elevation	1 (1.3%)
Dysesthesia	1 (1.3%)
Non-epileptic seizure	1 (1.3%)
Transient facial droop	1 (1.3%)
Increase in blood pressure and heart rate	1 (1.3%)
Any adverse event	66 (85.7%)

Table 3.—Response Based on Diagnosis

	All Patients n = 77	CM n = 63	NDPH n = 14
Acute responders	55 (71.4%)*	47 (74.6%)*	8 (57.1%)*
Sustained responders	15 (27.3%)	11 (23.4%)	4 (50%)

Significant results indicated by *.

difference of 4.628 (95% CI 3.99-5.27) ($P < .0001$), and 11 (23.4%) of acute responders met criteria for sustained response with mean difference of 2.136 (95% CI 0.91-3.37) $P < .0031$. Results in which the 95% CI dropped below 2 were interpreted as insignificant based off of our predefined criteria for acute and sustained responders (see Table 3).

Some patients received additional treatment in the course of hospitalization to augment the effect of ketamine. Other IV therapies included DHE n = 12 (15.6%), NSAIDs n = 28 (36.3%), and neuroleptics n = 40 (51.9%). One patient received IV steroids (not an acute responder), and another patient received greater occipital nerve blocks with local anesthetics (an acute responder). The number of patients receiving adjunctive therapies and their response status is depicted in Table 4.

DISCUSSION

Ketamine has been used as an acute treatment option for many types of pain. It may be a useful therapy in treatment of patients with medically refractory headaches. The mechanism by which prolonged ketamine infusion affects headache is uncertain, but may be modulated by blockade of NMDA receptors.[15] Ketamine reduces the response to repetitive painful stimuli, the "wind-up" effect, in animal models, which is felt to be an important cause of central sensitization and chronic pain in disorders such as migraine or fibromyalgia.[16] Our experience with subanesthetic ketamine infusion is in refractory patients seen at a tertiary headache center, all of whom had failed prior comprehensive inpatient admissions with aggressive treatment. The majority experienced acute benefit from ketamine infusions as reflected in the acute responder rate of 71.4%.

Other experience with subanesthetic ketamine has described common side effects of central nervous system excitation (delirium, hallucinations, agitation, dysphoria, and vivid dreams), sedation, and visual disturbance with quick resolution on cessation of treatment.[17] In light of these potential side effects, care must be taken in patient selection and monitoring in consideration of patients to undergo ketamine infusions. AEs among our patients were generally mild and resolved with decrease in ketamine dosage. Our experience would indicate that to ensure safety, patients must be monitored closely for fall risk, mood changes, and other central nervous system AEs. Vital signs must be monitored carefully for changes in heart rate or blood pressure. One patient did develop an asymptomatic elevation in liver enzymes. It is possible that more patients had asymptomatic rises as not all patients received repeat hepatic screening during the hospitalization.

Therapeutic use of ketamine has extended beyond traditional anesthetic applications. Recent reports on its use in treatment of refractory depressive symptoms have been explored in a case series of 6 patients with

Table 4.—Medications Used in Addition to Ketamine

	Acute Responders Receiving n (%)	Non-Responders Receiving n (%)
DHE	9 (16.4%)	3 (13.6%)
NSAIDs	24 (43.6%)	4 (18.2%)
Neuroleptics	30 (54.5%)	10 (45.5%)
Any additional medications	36 (65.5%)	12 (54.5%)

promising results.[18] A randomized, double-blind crossover study similarly found promising results in treatment of obsessive-compulsive disorder.[19] Within the field of headache medicine, a double-blind, randomized controlled study has shown benefit of intranasal ketamine in reducing the severity of aura in patients with migraine with prolonged aura.[5] Another group reported open label success using ketamine infusions in an outpatient clinic in 12 individuals with migraine. This report described a 3.5-point decrease in migraine severity on the 0-10 verbal rating scale following administration of IV ketamine averaging 64 mg administered over 159 minutes.[7] In the setting of use of ketamine outside of traditional labeling, caution is advised with concerns relating to long-term cognitive effects, dissociative and hallucinogenic potential, and possibilities of abuse and dependence.[20]

The greatest strength of our study is that we describe a relatively large population of patients with refractory headaches and have been able to determine significant acute benefit from a novel treatment option. Obvious limitations are related to the open-label, retrospective nature of the study in a narrowly defined population. The results may not be generalizable to more typical patients appropriate for routine inpatient management. Patients who are less refractory may be less willing to accept the numerous (albeit mostly non-serious) adverse events for what may be only a small, short-term benefit, if any benefit at all. We consider ketamine infusion an acute, rather than preventive treatment reserved for a very refractory population, and patients undergoing our ketamine treatments prior preventive therapy are typically continued through the infusion with minimal changes. In such refractory patients, it is typical for ongoing changes to occur in the plan of care that may impact the long-term response. It may be interesting to examine how many patients remained improved, or what medication changes may have occurred at discharge, but it is outside the scope of this exploratory retrospective analysis of our real world experience, and may be less meaningful since the variety of changes that occur would be challenging to categorize and generalize. Moreover, such analysis is only relevant to the sustained responder endpoint which did not achieve statistical significance. We expect changes to occur on an ongoing basis, but these changes (or lack thereof) do not consistently reflect whether a patient is stable, improved, or worse. Another significant limitation of this study is that other treatments were sometimes given along with ketamine thus making it challenging to determine the individual effects of treatment. However, as stated previously, this is a refractory, and frankly desperate, population of patients who already failed to respond adequately to inpatient treatment not involving ketamine, and what may have been required for some patients to improve is this unique combination of treatments including those that had not worked well in relative isolation in the past.

CONCLUSION

Despite these limitations, our experience provides some evidence that ketamine is a promising treatment for patients with severe headaches. Prospective, controlled studies would be useful in further investigating the efficacy of subanesthetic ketamine in headache patients. However, truly blinded studies are challenging with ketamine because it is difficult to mask the treatment effects. It could also be illuminating to investigate ketamine infusions in patients with less refractory headaches. Pending higher level evidence and given that ketamine is generally well tolerated, ketamine may be considered a reasonable acute treatment for well-selected headache patients for whom standard therapies are either ineffective or medically contraindicated. Future studies will be useful in further understanding long-term efficacy of ketamine in headache patients.

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